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Leveraging the Hydroarylation of α -(Trifluoromethyl)styrenes to Access Trifluoromethylated All-Carbon Quaternary Centers.

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KEYWORDS α -(trifluoromethyl)styrenes, hydroarylation, hexafluoroisopropanol, Brønsted acid, all-carbon quaternary centers.

ABSTRACT: α -(Trifluoromethyl)styrenes are attractive olefin building blocks that have eluded hydroarylation processes. Here we demonstrate that the use of a promoter system featuring triflic acid and hexafluoroisopropanol enables hydroarylation to directly build trifluoromethylated all-carbon quaternary centers. The observed reactivity significantly enriches the scope of hydroarylation of unactivated styrenes and provides straightforward access to trifluoromethylated diarylalkanes of interest. Gram scale reactions and further functionalizations illustrate the synthetic potential of this approach.

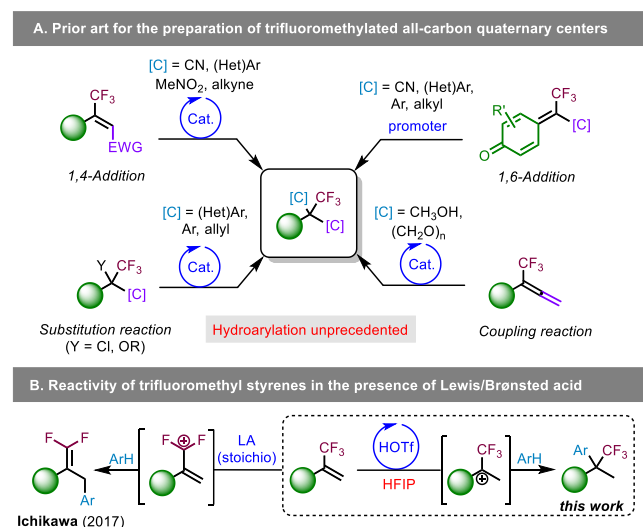
In the last two decades, the trifluoromethyl group has emerged as a key motif in drug discovery, crop science and materials science due its ability to reshape the properties of a parent molecule, notably its permeability, lipophilicity, and metabolic stability.¹ Hence, several elegant methods have been designed to introduce this group in a straightforward fashion.² Most of them rely on the installation of the trifluoromethyl group *via* different strategies such as nucleophilic, electrophilic, or radical trifluoromethylation.²

Recently, the direct functionalization of compounds in which the trifluoromethyl group is already pre-installed has become increasingly popular as a means of constructing trifluoromethylated all-carbon quaternary centers. An advantage of this approach is to rapidly build a large library of trifluoromethylated compounds from a single precursor by using different sets of carbon nucleophiles. Yet, to date, only a handful of transformations such as the 1,4-addition to activated alkenes,³ the 1,6-addition to *para*-quinone methides,⁴ the direct nucleophilic substitution of pre-activated α -trifluoromethyl alcohols,⁵ and coupling reaction with allenes have effectively used this strategy (Scheme 1A).⁶ An important limitation is that those methods often require tailored substrates that limit the scope of products that are attainable.⁷

In light of this, it was surprising to find that the hydroarylation of unactivated α -(trifluoromethyl)styrenes⁸ was unprecedented, which might be explained by the relative robustness of the alkene functional group when compared to the trifluoromethyl group. Indeed, in a seminal study by the group of Ichikawa on Lewis acid-promoted arylation of α -(trifluoromethyl)alkenes, only 3,3-difluoroallylated arenes were obtained,⁹ resulting from the activation of the CF₃ group (Scheme 1B). Similar trends have also been observed under transition metal catalysis¹⁰ and photocatalysis,¹¹ as well as with organolithium

reagents.¹² A hydroarylation process could facilitate the preparation of compounds incorporating trifluoromethylated all-carbon quaternary centers, offering at the same time more flexibility in terms of reaction scope since α -(trifluoromethyl)styrenes can be rapidly prepared in one step by Suzuki-Miyaura cross-coupling or Wittig reaction from either commercially available 2-bromo-3,3,3-trifluoro-1-propene or 2,2,2-trifluoroacetophenones (see Supporting Information for details). Such a reaction is, however, challenging. So far, there is only a single example of a hydrofunctionalization (hydroformylation) of α -(trifluoromethyl)styrenes with the introduction of a functional group at the α -position of the trifluoromethyl group.^{7b}

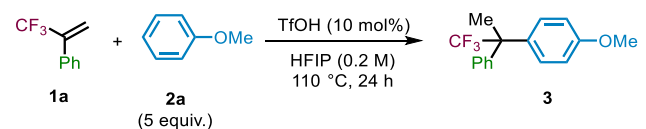
Scheme 1. Strategies towards the preparation of trifluoromethylated all-carbon quaternary centers



While the hydroarylation of unactivated styrenes has been extensively investigated,¹³ the hydroarylation of highly electronically deactivated styrenes remains underdeveloped. However, we have recently demonstrated that the acidity of self-assembled H-bond clusters of hexafluoroisopropanol (HFIP)¹⁴ could be amplified through coordination to a Lewis acid (Ca(NTf₂)₂/nBu₄NPF₆) or a Brønsted acid (TfOH) to trigger cationic reactions using highly deactivated substrates.^{15,16} Inspired by those results, our plan was to use such a combination to enable the first catalytic intermolecular hydroarylation of α -(trifluoromethyl)styrenes with readily available arenes as nucleophilic partners, thereby rapidly assembling trifluoromethylated diarylalkanes via the formation of a α -(trifluoromethyl) carbenium.¹⁷

We began our optimization studies with 1,1,1-trifluoromethylstyrene **1a** as a model substrate in the presence of TfOH as a catalyst (10 mol%) in HFIP (0.2 M) as a solvent (Table 1). By using anisole **2a** as an arene nucleophile, the target product **3** was obtained in 84% yield in the form of a separable 92:8 mixture of *para/ortho* regioisomers (entry 1). Reducing the temperature to 80 °C, the catalytic loading to 5 mol% or the number of equivalents of anisole resulted in decreased yields (entries 2-4). Increasing the concentration to 0.4 M proved to be detrimental to the reactivity (entry 5). Other Brønsted and Lewis acids such as HNTf₂,^{18,19} Ca(NTf₂)₂/nBu₄NPF₆,²⁰ B(C₆F₅)₃,²¹ Re₂O₇²² and Bi(OTf)₃²³ were tested but did not react or generate **3** in a synthetically useful yield (entries 6-10). On the other hand, the combination of Bi(OTf)₃/nBu₄NPF₆ afforded **3** in 71% yield (entry 11).

Table 1. Optimization of reaction conditions



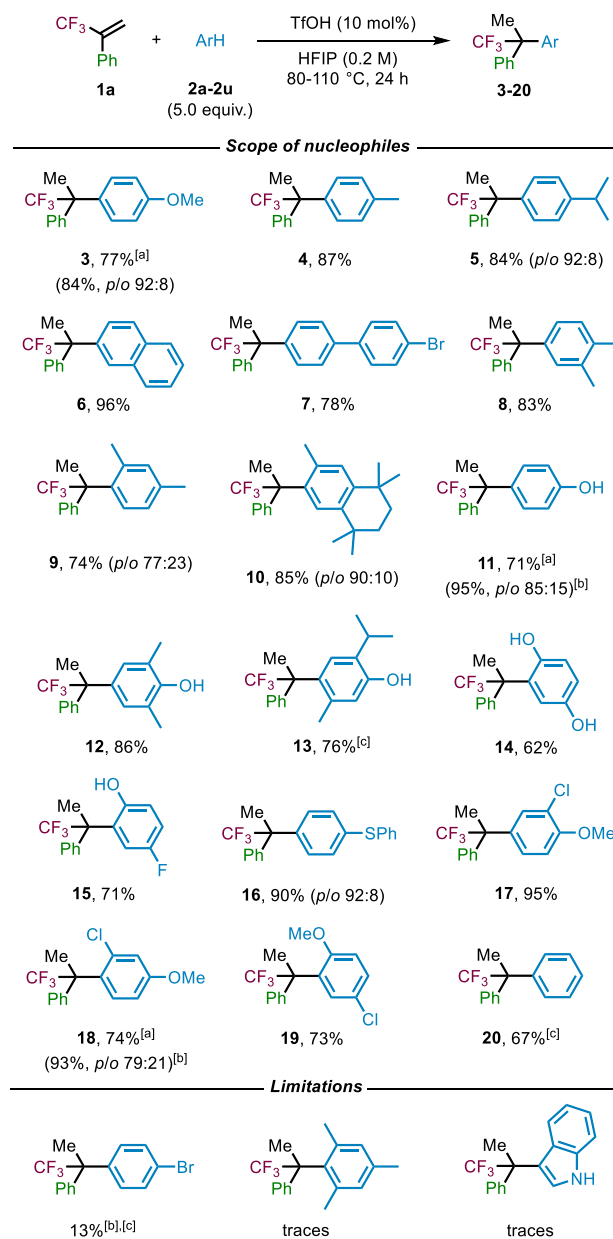
Entry	Variation from standard conditions ^[a]	Yield ^[b] (%) (<i>p/o</i> ratio)
1	none	84 (92:8), 79^[c]
2	80 °C instead of 110 °C	73 (88:12)
3	5 mol% of TfOH instead of 10 mol%	55 (86:14)
4	3 equiv. of 2a instead of 5 equiv.	60 (92:8)
5	0.4 M instead of 0.2 M	64 (92:8)
6	HNTf ₂ instead of TfOH	16 (87:13) ^[d]
7	Ca(NTf ₂) ₂ /nBu ₄ NPF ₆ instead of TfOH	5 (87:13) ^[d]
8	B(C ₆ F ₅) ₃ instead of TfOH	n.r.
9	Re ₂ O ₇ instead of TfOH	traces
10	Bi(OTf) ₃ instead of TfOH	33 (87:13)
11	Bi(OTf) ₃ /nBu ₄ NPF ₆ instead of TfOH	71 (87:13)
12	TFE instead of HFIP	5 (83:17) ^[d]
13	1,2-DCE instead of HFIP	7 (82:18) ^[d]
14	MeNO ₂ instead of HFIP	- ^[e]
15	toluene instead of HFIP	traces
16	without TfOH	n.r.

[a] Standard reaction conditions: **1a** (0.2 mmol), anisole (5.0 equiv.), TfOH (10 mol%) in HFIP (0.2 M), 110 °C, 24 h (in a sealed tube). [b] Isolated yield. [c] 5.0 mmol scale. [d] NMR yield using triethylsilane as an external standard. [e] A mixture of several products was observed.

Other common organic solvents were unable to provide **3** (entries 12-15), highlighting the crucial role of HFIP in this reaction. Finally, a control reaction in the absence of TfOH was conducted, and no product was observed (entry 16). From a practical point of view, upscaling the reaction (5.0 mmol) allowed a gram-scale synthesis of the trifluoromethylated compound **3** in 79% yield (3.96 mmol, 1.11 g) (entry 1).

With those reaction conditions in hand, we proceeded to investigate the scope of this reaction, initially focusing on the reactivity of various electron-rich arenes with **1a** (Scheme 2). In most cases, the reaction was achieved in high

Scheme 2. Scope of arenes **2a-2u** with 1,1,1-trifluoromethylstyrene **1a**

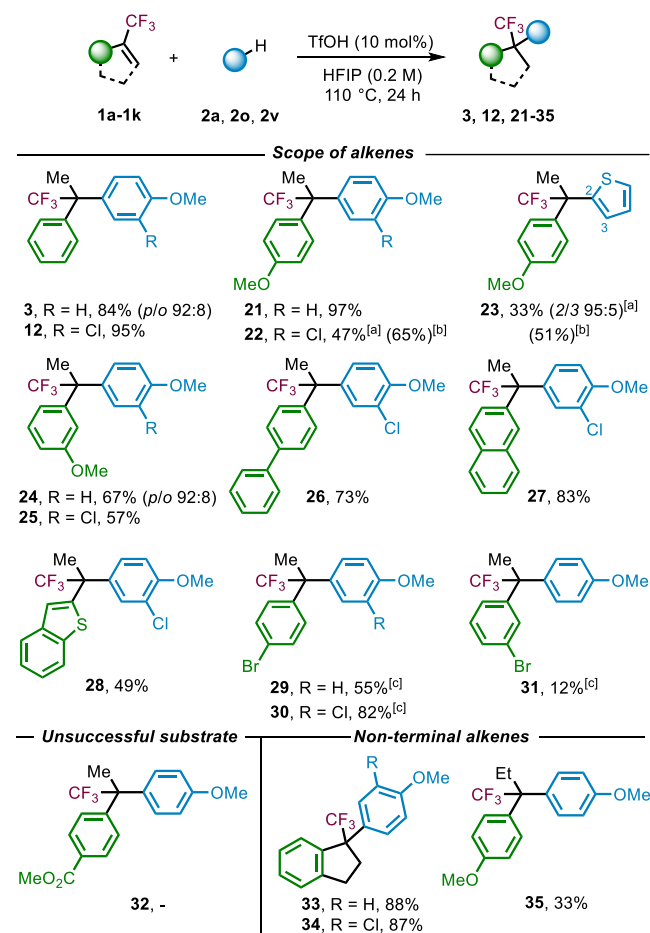


[a] Isolated yield of the major regioisomer. [b] NMR yield and ratio *p/o* using triethylsilane as an external standard. [c] Reaction temperature 80 °C.

yields (up to 96%), along with an excellent regioselectivity. Toluene (**4**), cumene (**5**), naphthalene (**6**),²⁴ biphenyl (**7**), xylene (**8-9**), tetrahydronaphthalene (**10**), phenol (**11-15**) and sulfide (**15**) derivatives were among the arene nucleophiles compatible with our standard conditions. Moreover, the combination of a donor substituent (OMe) with a moderate electron-withdrawing group (Cl) yielded the corresponding products in high yields (**16-18**, 70-95%). In several cases, regioisomers could be separated by flash column chromatography. Importantly, less nucleophilic arenes such as benzene (**20**, 67%) also proved to be competent nucleophiles for this transformation. In turn, an electron-poor (bromobenzene) or a sterically hindered arene (mesitylene) reacted poorly under the reaction conditions, leading to a slow decay of the substrate **1a** over time. The same observation was made with when indole was used as nucleophile.

Next, we examined the scope of trifluoromethylated styrenes using anisole **2a**, 1,2-chloroanisole **2o**, and thiophene **2v** as nucleophiles (Scheme 3). The reaction was compatible with electron-donating substituents at the *para*

Scheme 3. Scope of 1,1,1-trifluoromethylated styrenes **1a-1k**

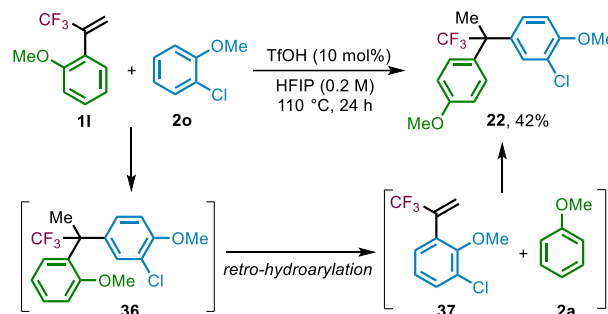


[a] Isolated yield. [b] NMR yield using triethylsilane as an external standard. [c] Reaction temperature 80 °C. [d] Reaction time 48 h in the presence of 20 mol% of TfOH.

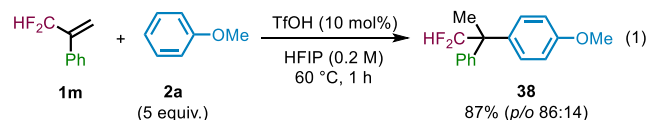
and *meta* position, delivering products **21-25** in yields ranging from 33 to 97%. In some cases (**22** and **23**), products bearing two electron-rich arenes were prone to retro-hydroarylation upon purification by flash column chromatography, leading to diminished yields. Other electron-rich (hetero)arenes such as biphenyl (**26**, 73%), naphthalene (**27**, 83%) and benzothiophene (**28**, 49%) were also amenable to the reaction, as well as moderate electron-poor arenes such as aryl bromides (**29-31**, 12-82%). However, in the case of substrates incorporating an arene bearing an electron-withdrawing group, such as an ester (**32**), the substrate remained intact as it is likely too electronically deactivated to react. We then turned our attention to non-terminal alkenes. In the case of indene **1j**, trifluoromethylated indanes **33** and **34** were obtained in high yields (88% and 87%, respectively).²⁵ In turn, an acyclic trisubstituted alkene also provided the target product **35**, albeit in a moderate yield (33%), which is the result of a competitive hydroarylation at the other position of the alkene (30% yield).

Of note, the presence of an *ortho*-OMe substituent posed complications, as the hydroarylation becomes reversible under the reaction conditions. For example, using **2o** as arene nucleophile led to a 42% yield of the re-arranged product **22**, arising from a retro-hydroarylation of the *o*-methoxyphenyl moiety and its subsequent alkylation at the *para* position with the newly formed styrene **37** (Scheme 4).

Scheme 4. Retrohydroarylation with substrate **1l**



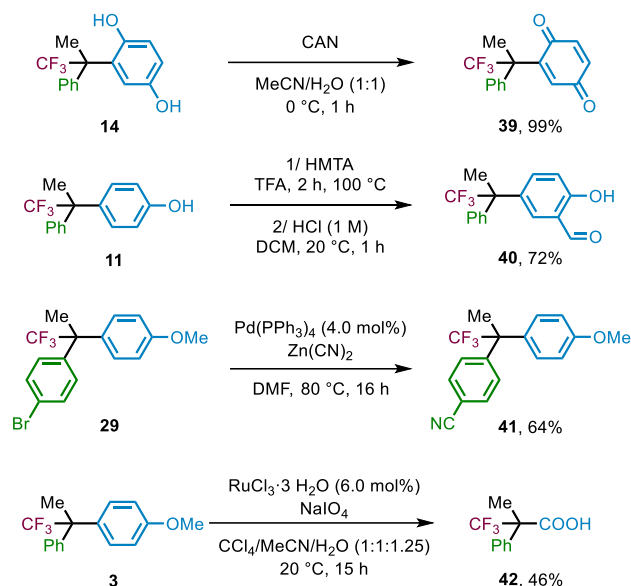
Importantly, this transformation is not limited to a CF₃ group but could be extended to the CF₂H group,²⁶ whose properties differ from the CF₃ group.²⁷ In the case of substrate **1m**, the reaction with anisole led to the product **38** in 87% (*para/ortho* 86:14). It is noteworthy that the difluoromethyl analog is far more reactive as the reaction was achieved in only 1 h at 60 °C.



To illustrate the synthetic utility of this transformation, several derivatizations were carried out to introduce functional groups of interest (Scheme 5). For instance, the oxidation of 1,4-benzenediol **14** was conducted in the presence of cerium ammonium nitrate (CAN) to deliver quinone **39** in a nearly quantitative yield. In addition, the regioselective formylation of phenol **11** was achieved in

72% yield (**40**) by using the Duff reaction.²⁸ As mentioned above, the hydroarylation reaction was not compatible with substrates that are deactivated by the presence of a second electron-poor functional group; however, this issue may be circumvented by a palladium-catalyzed cross-coupling reaction between bromobenzene **29** and zinc(II) cyanide (**41**, 64% yield). In another application, the *p*-methoxyphenyl group of **3** can be used as a masked carboxylic acid *via* oxidation (**42**, 46%),²⁹ thereby mimicking the hydrocarboxylation of 1,1,1-trifluoromethylstyrene **1a**.

Scheme 5. Derivatizations of trifluoromethylated compounds



To gain insights into the mechanism of the reaction, DFT computations were performed on the reaction of **1a** with benzene at the SMD(HFIP)/MN15/def2-TZVP level of theory (Figure 1).³⁰ Protonation of **1a** by HOTf can either yield the carbenium ion **1a-H⁺** or, via significantly less favorable HF elimination, the difluorocarbenium ion **A**. The large energy difference computed for the formation of **1a-H⁺** and **A** is in agreement with our experimental findings that only products originating from **1a-H⁺** were experimentally obtained and not those resulting from HF elimination via cation **A**. Though formation of cation **A** from **1a-H⁺** is unfavorable under our conditions, stoichiometric addition of a Lewis acid that binds fluoride can provide the driving force for the selective formation of **A** as reported by Ichikawa.^{9a} Once formed, **1a-H⁺** can react with multiple available nucleophiles in solution. The reactions with triflate or HFIP to yield the trapping products **1a-OTf** and **1a-HFIP**, respectively, are computed to be only slightly exergonic and are thus expected to be reversible.³¹ Nucleophilic addition of benzene to the carbenium ion **1a-H⁺** proceeds via a moderate activation barrier relative to the carbenium ion (+48.9 kJ mol⁻¹) to yield the Wheland intermediate. Deprotonation of this intermediate by any available base regenerates the acid catalyst and yields the final product **20**, thus closing the catalytic cycle.

Finally, we compared the cation **1a-H⁺** with the cumyl cation **C**. Starting from HOTf and either **1a** or α -methylstyrene, the

Gibbs free energies for the formation of the carbenium ions are +72.6 or -3.2 kJ mol⁻¹, respectively, suggesting that the formation of **1a-H⁺** is significantly more endergonic. However, once formed **1a-H⁺** is a significantly stronger electrophile than **C**: In the reaction with benzene, **1a-H⁺** reacts via a 32.6 kJ mol⁻¹ lower activation barrier than cation **C** (for the full Gibbs energy profile starting from α -methylstyrene, see Supporting Information, Figure S2). The different stability of **1a-H⁺** and **C** is furthermore illustrated by gas-phase methyl anion affinities (ΔG_{MA} , calculated at the B3LYP/6-311++G(3df,2pd)//B3LYP/6-31G(d,p) level). Methyl anion affinities are an established tool to compare cation stabilities and have previously been computed for a wide range of benzhydrylium ions that are standard tools in carbocation chemistry.³² While the cumyl cation is found to have a similar ΔG_{MA} compared to the parent benzhydrylium

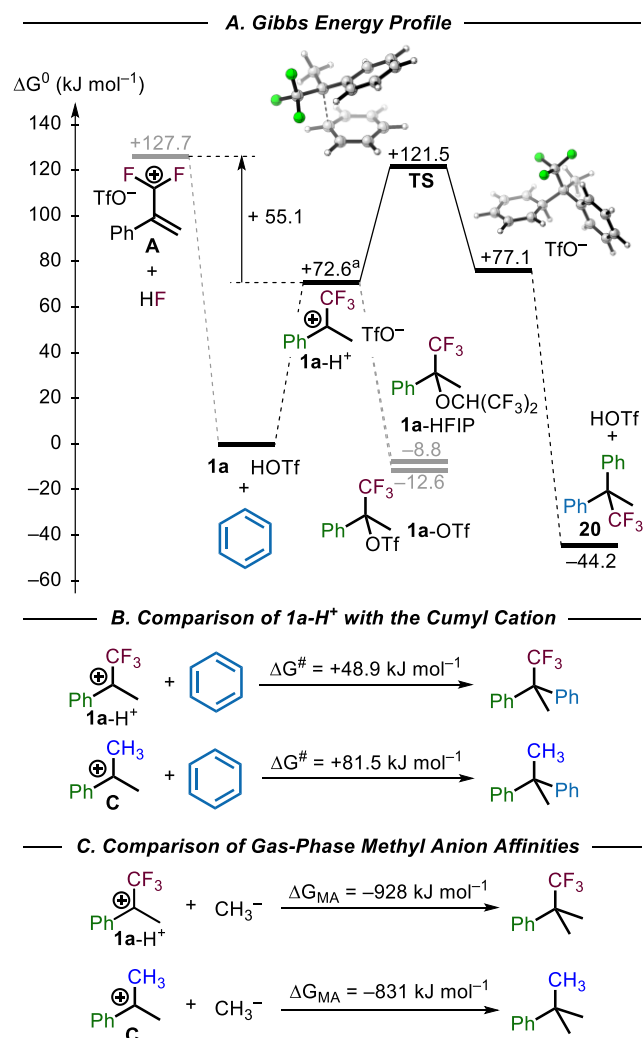


Figure 1. (A) Gibbs energy profile calculated at the SMD(HFIP)/MN15/def2-TZVP level of theory and (B) comparison of the activation barriers for benzene addition of **1a-H⁺** and the cumyl cation **C** at the same level. (C) Gas-phase methyl anion affinities (ΔG_{MA}) calculated at the B3LYP/6-311++G(3df,2pd)//B3LYP/6-31G(d,p) level. ^a When using one explicit HFIP molecule on both TfOH and TfO⁻, an insignificantly different value of +73.6 kJ mol⁻¹ was obtained for the formation of **1a-H⁺** starting from **1a**.

ion Ph₂CH⁺ ($\Delta G_{MA} = -827.3 \text{ kJ mol}^{-1}$), the value obtained for cation **1a-H**⁺ is higher than for any of the benzhydrylium ions previously characterized (see Supporting Information, Figure S3 for a comparison).³² This furthermore illustrates the unusually high instability and thus reactivity of cation **1a-H**⁺ compared to more classical carbenium ions and the abilities of HFIP to enable its formation. One potential role of HFIP in mediating this transformation might again be in reversibly trapping the carbenium ion **1a-H**⁺ e.g. in the form of **1a-HFIP**, thus preventing potential oligomerization of **1a** observed in its absence.³⁰

In conclusion, we herein presented a new hydroarylation reaction that directly forms trifluoromethylated all-carbon quaternary centers. This method relies on the unique combination of TfOH and HFIP to promote the target reaction, whose mechanism was rationalized by DFT computations. This reaction is facile to operate, scalable and provides most of the products in high yields and with good regiocontrol. The compounds obtained can serve as a platform to access more complex molecules. Therefore, we anticipate that this new route to trifluoromethylated compounds will open new opportunities in drug discovery.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge via the Internet at <http://pubs.acs.org>. Experimental procedures, characterization data, copies of NMR spectra, procedure of quantum-chemical calculations and xyz coordinates of all optimized structures (PDF)

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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